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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,743	01/16/2002	Jennifer L. Hillman	PF-0509 US	5333
27904	7590	05/26/2004	EXAMINER	
INCYTE CORPORATION EXPERIMENTAL STATION ROUTE 141 & HENRY CLAY ROAD BLDG. E336 WILMINGTON, DE 19880			ZEMAN, ROBERT A	
			ART UNIT	PAPER NUMBER
			1645	
DATE MAILED: 05/26/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/674,743

Applicant(s)

HILLMAN ET AL.

Examiner

Robert A. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 February 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-34 is/are pending in the application.
- 4a) Of the above claim(s) 21,25,27,28 and 30-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22-24,26 and 29 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 21-34 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

The amendment and response filed on 2-24-2004 are acknowledged. Claims 21-34 are pending. Claims 21, 25, 27-28 and 30-34 remain withdrawn from consideration. Claims 22-24, 26 and 29 are currently under examination.

Claim Rejections Withdrawn

Claims 22-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 22-24 and 26 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by being dependent on a non-elected claim (claim 21) is withdrawn in light of the amendment thereto.

Claim Rejections Maintained and New Grounds of Rejection

35 U.S.C. First Paragraph, Enablement Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 22-24, 26 and 29 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding polypeptides having a sequence comprising SEQ ID NO:5 (SEQ ID NO:70 and its equivalents due to codon degeneracy), does not reasonably provide

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enablement for the myriads of other polynucleotide species claimed is maintained for reasons of record. The specification is enabling only for claims limited to polynucleotides encoding polypeptides represented by SEQ ID NO:5 and polynucleotides represented by SEQ ID NO:70 because the specification does not reasonably provide enablement for polynucleotides encoding polypeptide variants having at least 90% sequence identity to SEQ ID NO:5 or polynucleotides with at least 90% sequence identity to SEQ ID NO:70. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The amended claims are drawn to polynucleotides encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:5, a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence recited in SEQ ID NO:5, a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:5 and an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:5. Said polypeptides have no claimed biochemical, immunological or physiological function.

Applicant argues:

1. Independent claim 22 recites not only that the variant polynucleotides encode polypeptides that are at least 90% identical to SEQ ID NO:5, they also have a “naturally occurring amino acid sequence”.
2. Given the information provided by SEQ ID NO:5 and SEQ ID NO:70, one of skill in the art would be able to routinely obtain a polynucleotide comprising “a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:5” or “a

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polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:70”.

3. Identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques.

4. One need not make and test vast numbers of polypeptides that are based on the amino acid sequence of SEQ ID NO:5, one of skill in the art only need screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides/polypeptides that already exist in nature.

5. The documents cited by the Examiner relating to structure-function relationships in proteins (Bowie et al.) and the alleged difficulties in assigning protein function based on homology comparison are not germane since regardless of the precise functional characteristics of the SEQ ID NO:5 and SEQ ID NO:70 variants, one can still make the claimed polypeptide variants using the disclosure provided by the present specification.

6. The claimed polynucleotides can be used in diagnostic testing, drug discovery, expression profiling etc.

7. Brenner et al. (PNAS (1998) 95 : 6073-6078) disclose that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues and that $\geq 40\%$ identity over at least 70 residues is reliable in signifying homology between proteins. Hence, based on Brenner, one would expect all the claimed “ 90% variants” to have the functional activities of a HTRM protein.

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8. None of the references cited by the Examiner contradicts Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1-4, the limitation "naturally occurring amino acid sequence at least 90% identical to" SEQ ID NO:5 or SEQ ID NO:70 is not a limitation of all the polypeptides encoded by the claimed polynucleotides. Moreover, it is impossible to determine which "variants" would be considered "biologically active" if, as Applicant asserts, one does not need to know the function or structure of a given polypeptide in order to be able to meet the enablement requirements.

With regard to Points 5-6, even if, for the sake of argument, Applicant's assertion that one of ordinary skill in the art could readily "make" the claimed polynucleotides, the specification does not give any direction on how to "use" a given polynucleotide. Contrary to Applicant's assertion that the claimed polynucleotides cannot be used in diagnostic testing, drug discovery, expression profiling etc. (point 6) unless one knows the structure/function of the encoded polypeptide. Applicant is reminded that the requirements under 35 U.S.C. 112, first paragraph, require the specification enable any person skilled in the art to which it pertains or with which it is most nearly connected, to **make and use** the invention commensurate in scope with these claims.

With regard to Points 7-8, Brenner et al. discloses methods of determining whether "proteins whose relationships are known reliably known from their structures and functions" are **evolutionary homologs** (see abstract). Brenner et al. does not teach that you can accurately

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predict the activity/function of a protein based on its sequence homology to another protein. Moreover, contrary to Applicant's assertion, Brenner et al. does not disclose that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. In fact, Brenner discloses (at best) that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability that two **known** proteins are evolutionary homologs.

Therefore as outlined previously, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J. of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al. (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of

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aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, proteins with up to 10% dissimilarity, to the polypeptides of SEQ ID NO:5 that maintained the characteristics of the polypeptides encoded by SEQ ID NO:5 could not be predicted. Additionally, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, column 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, column 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, column 3). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, column 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399, paragraph bridging columns 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those features are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, paragraph bridging cols 1 and 2). Clearly, given not only the teachings of Bowie et al., Lazar et al. and Burgess et al. but also the limitations and pitfalls of using computational

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sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, the claimed proteins could not be predicted based on sequence identity to SEQ ID NO:5 or SEQ ID NO:70. Further, even if a given polypeptide possesses all the structural limitations of the claimed invention, neither the specification nor any art of record teaches what that polypeptide is, what it does, does not teach a relationship to any specific disease or establish any involvement of the polypeptide in the etiology of any specific disease or teach which fragments might be active or which derivatives would function as claimed in a pharmaceutical composition. Clearly, it could not be predicted that a polynucleotide, or a variant, that encodes a protein that shares only partial homology with a disclosed protein or that a protein that is encoded by a "variant" of a given SEQ ID NO: will function in a given manner. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use the claimed polynucleotides. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

35 U.S.C. 112, Written Description Rejection

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The rejection of claims 22-24, 26 and 29 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for reasons of record.

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The amended claims are drawn to polynucleotides encoding a polypeptide comprising an amino acid sequence of SEQ ID NO:5, a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence recited in SEQ ID NO:5, a biologically active fragment of a polypeptide having an amino acid sequence of SEQ ID NO:5 and an immunogenic fragment of a polypeptide having an amino acid sequence of SEQ ID NO:5. Said polypeptides have no claimed biochemical, immunological or physiological function.

Applicant argues:

1. The written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one of skill in the art. SEQ ID NO:5 and SEQ ID NO:70 are specifically disclosed in the specification.
2. The instant claims specifically define the claimed genus through the recitation of chemical structure.
3. The instant claims do not define a genus which is highly variant”.
4. The state of the art at the time of the present invention is further advanced than at the time of the Lilly and Fiers applications. Therefore given the sequence information of SEQ ID NO:5 and SEQ ID NO:70 and the **additional extensive detail** provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of the invention.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1-3, the limitation “naturally occurring amino acid sequence at least 90% identical to” SEQ ID NO:5 or SEQ ID NO:70 is not a limitation of all the polypeptides encoded by the claimed polynucleotides. Moreover, since it is impossible to determine which

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"variants" would be considered "biologically active" if, as Applicant asserts, one does not need to know the function or structure of a given polypeptide in order to be able to meet the written description requirements. Hence, contrary to Applicant's assertion, the claimed genus is highly variant.. As pointed out by Applicant,

An applicant may also show that an invention is complete by the disclosure of **sufficiently detailed**, relevant identifying characteristics which provide evidence that an applicant was in possession of the claimed invention, i.e. **complete or partial structure**, or other physical and/or chemical properties, **functional characteristics** when coupled with a known or disclosed correlation between function and structure or some combination of such characteristics.

In the instant case, the specification discloses neither a complete or partial structure of the claimed "variants" nor any functional characteristics for the claimed variants.

Therefore, as outlined previously, the specification discloses SEQ ID NO:5 and SEQ ID NO:70 that corresponds to a human transcriptional regulator molecule (HTRM). SEQ ID NO:5 and SEQ ID NO:70 meet the written description provision of 35 USC 112, first paragraph. However, the aforementioned claims are directed to encompass, sequences that have at least 90% identity to SEQ ID NO:5 (claims 22-24 and 26) or SEQ ID NO:70 (claim 29), corresponding sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:5 and SEQ ID NO:70, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the

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complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

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Therefore, only SEQ ID NO:5 and SEQ ID NO:70, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Additionally, absent factual evidence, a percentage sequence similarity of less than 100 % is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of such a similar known biomolecule. It is known for nucleic acids as well as proteins, for example, that even a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many instances, albeit not in all cases. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. Therefore, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed biomolecule and the indicated similar biomolecule of known function and therefore lacks support regarding utility and/or enablement.

Claims 22-24, 26 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is rendered vague and indefinite by the use of the phrase “comprising **an** amino acid sequence of SEQ ID NO:5”. The term “an” implies that there is more than 1 sequence encompassed by SEQ ID NO:5. Consequently it is impossible to determine the metes and bounds of the claimed invention.

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Claim 22 is rendered vague and indefinite by the use of the term “biologically active”. It is unclear what processes the claimed fragment must be able to perform in order to meet the limitations of the instant claim.

Claims 22 and 29 are rendered vague and indefinite by the use of the term “naturally occurring” amino acid/polynucleotide sequence. What constitutes a naturally occurring sequence? How does one determine whether a given sequence is “naturally occurring” or not?

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866.

The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Zeman
May 18, 2004


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